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What the clinician wants to know: radiation oncology perspective

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Abstract

The delineation of the target volume, i.e. the volume which should be irradiated with a therapeutic dose of irradiation, is of utmost importance in radiotherapy. Modern imaging techniques cannot be missed in this process. Diagnosticians and radiation oncologists therefore should understand each other's needs and potential.

Keywords: *Radiotherapy; treatment planning; target volumes; biological target volume.*

Staging for radiotherapy

Radiotherapy like surgery is a treatment for locoregional tumour growth. So, imaging modalities are extremely important for staging. Computerized tomography (CT), ultrasonography and magnetic resonance imaging (MRI) are used in the work-up of many tumours, e.g. in cervical cancer and head and neck tumours to detect lymph nodes, in rectal cancer to judge whether a free margin can be obtained to make the patient a suitable candidate for short term irradiation followed by surgery. New imaging modalities are also being introduced for staging such as fluorodeoxy glucose positron emission tomography (FDG-PET) scanning in lung cancer and MR lymphography with nanoparticles in prostate cancer.

Image guided radiotherapy volumes

Whereas surgery is tumour eradication under direct vision, radiotherapy is tumour eradication under indirect vision. So, imaging is of extreme importance for radiotherapy planning. In radiation oncology the target volume is that part of the body where a therapeutic dose of irradiation should be applied. This target volume is subdivided into several subsets: the gross tumour target volume (GTV), the clinical target volume (CTV) and the planning target volume (PTV). The GTV and CTV have a biological background. The GTV is what you can see, measure or palpate. The CTV is the suspected microscopic extension of the disease, and as in surgery, radiation oncologists also take a margin around the visible tumour. The GTV can include regional lymph nodes when microscopic spread to lymph nodes is expected; and when they should be treated electively, one could consider this as a nodal CTV. The PTV is a geometric and not a biological concept. This volume by two margins takes into account organ movement (internal margin) and positioning in accuracies and inaccuracies of the irradiation delivering equipment (set-up margin). The PTV is created to ensure that the therapeutic dose is indeed delivered to the CTV.

Although one could imagine that the delineation of the GTV is most simple, we have to realise that different imaging modalities 'see' tumours or organs differently, e.g. the size of the prostate is different on MRI than CT. What is the truth? Often radiation oncologists use both. Consequently image registration or image fusion has become of paramount importance. Like surgery, in radiotherapy we also do some harm to normal tissues. Healthy tissue is unavoidably irradiated. However, the radiation dose in these tissues should be kept below tolerance which means below the dose which creates clinically manifest severe damage. For this reason a fourth volume in the irradiated part of the body has to be taken into account: the volume around an organ at risk. This is the planning organ at risk volume (PRV). For

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example, when very high doses are given to the prostate, one has to identify the PRV of the rectum. With the use of so-called dose volume histograms, an impression can be obtained of the percentage of the rectum receiving a certain percentage of the total dose which correlates with the risk of complications.

Volume delineation

To define the target volumes many radiotherapy departments now use their own dedicated CT scanners. One has to realize that these scanners are different from diagnostic ones. They have a larger aperture to allow for scanning in treatment position and they have a flat table top. Also the scanning protocols can be different from the diagnostic ones. Planning scans are performed without the use of contrast so as not to disturb the physiological size and density of some of the organs. Scanning times might be different, e.g. slower to detect lung movements and also the slice distance may be different, usually 3 mm, to obtain a reliable digitally reconstructed radiograph (DRR). So, planning scans are not diagnostic scans and one should be careful about using them for diagnostic purposes. Furthermore, diagnostic scans are not planning scans and one should be careful about using them without certain precautions for treatment planning.

Intensive collaboration between the imaging departments and radiotherapy departments is necessary nowadays for radiation oncology. It would be advisable to collaborate with a dedicated diagnostician who understands the needs of the radiation oncologist. Proper diagnostic reports should contain the information of importance for the radiation oncologist, meaning that the slices on which the GTV can be seen should be mentioned in the diagnostic report. On the other hand, the radiation oncologist should increase his/her knowledge in diagnostic imaging by additional training as resident and as part of a CPD (continuing professional development) programme. Because different types of images are used and have to be matched with the planning CT slices, image registration has become an important part of the volume delineation process. Image registration can be performed by the use of anatomical landmarks but also with the use of gold markers which are used in prostate cancer GTV delineation.

Apart from the dedicated planning CT scanners, radiation oncologists also make use of a simulator consisting of a traditional X-ray apparatus, in some cases provided with a CT extension with which low quality CT slices can be made; these are sufficient for the contouring of the patient. Essential in all these simulation or localization procedures is that the images are acquired in relation to a three-dimensional (3-D) set of co-ordinates. Skin markers make it possible to position the patient in a reproducible manner, making it possible to deliver the treatment dose in a large number of fractions over a substantial overall treatment time, e.g. 35 fractions in 7 weeks. Dose plans finally are created on the basis of the delineated volumes in relation to the co-ordinates.

Biological image guided radiotherapy

The tumour cell density might not be the same throughout a tumour or an organ with a tumour. To date in the treatment of prostate cancer the whole organ is treated with a homogeneous dose while in many patients one could identify a dominant intratumoral lesion (DIL) with modern imaging techniques. It is logical to suppose that the irradiation dose in the DIL should be higher than in the rest of the prostrate and so a fifth volume can be introduced: ‘the biological target volume’ (BTV).

Similarly, areas with other biological properties could be identified such as hypoxic areas or rapidly proliferating areas in order to adapt the dose distribution accordingly. A new horizon is looming for all kinds of biological imaging using new isotopes for PET scanning and with the use of MR spectroscopy. Combined PET/CT scanners could facilitate the necessary image registration with reference to the co-ordinates. The developments in imaging techniques and radiotherapy equipment have written the history of radiotherapy in the past 30 years, from an uncontrolled inhomogeneous dose distribution via a controlled homogeneous distribution towards a controlled inhomogeneous dose distribution in biological image guided radiotherapy.

Target volume delineation on breast cancer and breast cancer treatment

The role of radiotherapy in breast cancer is as an adjuvant to surgery. Either the breast is removed by mastectomy or the tumour only as part of a breast conserving procedure. Consequently, the target volume only is a CTV. In breast conserving therapy the tumour bed after lumpectomy usually receives a higher dose. The visualization of this tumour bed is still not optimal and usually the only way is the use of radio-opaque clips which can interfere with follow-up MRI scans. Research to develop better methods is urgently required.

Conclusion

In the second half of the last century radiology in many countries split into radiotherapy and radiodiagnostics and imaging as independent specialties. Today the interaction of our disciplines is more intensive than ever which creates the need to understand each other’s needs and potential.

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The sentinel node in breast cancer: an update

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Abstract

There has been rapid acceptance of sentinel lymph node biopsy into the management of breast cancer over the past 10 years. This article seeks to highlight the controversies and to summarise its current status.

Keywords: *Sentinel lymph node; breast cancer.*

Introduction

The prognosis of breast cancer is determined primarily by axillary lymph node status[1–3]. Axillary lymph node dissection (ALND) surgery carries a significant morbidity with complications such as lymphoedema, pain, numbness and limited shoulder movement[4–6]. The sentinel node is the first draining node on the direct drainage pathway from the primary tumour site[7]. If the sentinel node is positive there is a 40% risk that higher order nodes may also be involved with metastatic disease[8]. Sentinel lymph node biopsy (SLNB) is a minimally invasive alternative to ALND for nodal staging in breast cancer. The technique assumes orderly progression of tumour spread to the regional nodes; and biopsy of the first node in the lymphatic chain at risk for metastasis should therefore reflect involvement of the remaining nodes. Although no results from randomised trials validating SLN biopsy in breast cancer are yet available, excellent clinical outcomes using different protocols have been achieved in over 20 000 patients studied to date[8]. Comparison of the results of SLNB with ALND has shown that the sentinel node is representative of the presence or absence of metastases in the remainder of the nodal basin (with a false negative rate of less than 2% in most series)[9–13]. Other prospective studies have also validated the concept[14–18].

Technical issues

Lymphoscintigraphy

A large choice of dyes and radiopharmaceuticals (usually ^{99m}Tc sulphur colloid) are available. The colloid employed should be of a size to be taken up efficiently and retained within the sentinel node. It has been shown that the highest counts in recovered sentinel nodes were from 100–200 nm albumin colloid particles[19]. Filtered ^{99m}Tc sulphur colloid (100 nm filtered) has a faster transport rate to the regional nodes and lower radiation dosimetry. As a result it is the preferred choice if performing surgery within 2 h of injection[8]. The sentinel node is more successfully identified with radiopharmaceuticals than with dyes but a combined technique using both maximises the potential of accurate staging[15,20–22]. Preoperative lymphoscintigraphy enables faster location of radioactive nodes at surgery and the combined approach results in identification and harvesting of more nodes[23,24]. The injection technique seems to matter little as axillary nodes stained blue by intradermal, peritumoural, subdermal, periareolar and subareolar injections identify the same nodes[21,25–27]. It also appears that there is often more than one sentinel lymph node and using dual agents will assist in identifying all sentinel nodes. In a prospective multi-institutional study of 1436 patients, the false negative rate was 14.3% if a single sentinel lymph node was removed compared with 4.3% if multiple sentinel lymph nodes were removed indicating that there is often more than one sentinel node[28]. Despite variation in mapping techniques results have been similar worldwide with sensitivity and diagnostic accuracy rates greater than 95% and false negative rates ranging from 0 to 10%[29]. Some breast cancer programmes do not routinely utilize preoperative lymphoscintigraphy because of the added time, expense and the fact that the surgical decision making can be performed intraoperatively[8]. Others advocate the concept of the triple technique comprising preoperative lymphoscintigraphy, and injection of radiotracer with the use of a hand probe and blue dye[30]. Variables such as availability of resources, patient numbers, level of competence and local working practices mean that no standard protocol exists. Nonetheless, it is recognised that identification of the sentinel node in greater than 96% of patients and a false negative rate

of less than 5% is a desirable outcome[10,31,32]. Using lymphoscintigraphy the surface location of the sentinel node can be marked with some centres marking all sentinel nodes visualised[33,34]. Although high resolution collimators should be used, a medium energy collimator will suffice[34]. The camera is placed as close to the patient as possible and images should be acquired in at least two planes. If the site of injection is close to the nodes, shielding may be necessary to visualise the sentinel node. In one centre analysing the results of 640 patients, 94% demonstrated a sentinel node in the ipsilateral axilla but 46% also had sentinel nodes outside the axilla[34]. The most important site of extra-axillary drainage was to the internal mammary nodal chain and 40% of patients demonstrated a sentinel node in this area[34]. In 5% of patients, drainage was exclusively to extra-axillary sentinel nodes. Preoperative lymphoscintigraphy enables these nodes to be identified.

Site of injection

Several theories exist concerning lymph node drainage in the human breast[35]. Although Sappey described flow to the subareolar plexus and then to the axilla, this view was not universally accepted[36]. An alternative drainage pattern proposed direct drainage to the ipsilateral axilla avoiding the subareolar plexus[35,37]. A recent study of 145 dynamic lymphoscintigrams using both intraparenchymal and subdermal injections was unable to visualise the subareolar plexus indicating that it may not act as a conduit to the ipsilateral axilla[38]. Variable drainage patterns from injections of localising agents into the subareolar plexus, subdermal breast tissue and the deep breast parenchyma have been demonstrated by several groups[39–42]. Seven sites of injection have been described (peritumoural, subdermal, periareolar, intratumoural, intradermal, subareolar and subtumoural) and one of the factors dictating choice is the intention to locate internal mammary nodes in addition to axillary nodes[43]. Peritumoural injections were the first type of injection used[44,45]. Some groups claim better success with intradermal injections than with peritumoural technique when sulphur colloid and blue dye are used[46]. Internal mammary node drainage occurs in a significant proportion after peritumoural injection but not after intradermal injection[47]. However, the intradermal technique has been shown to identify the SLN in the axilla with a frequency of 98% compared with 90% for peritumoural parenchymal technique[10,48]. Periareolar injections are made just outside the areolar border at four equally spaced sites. The injections are subdermal though a single subareolar injection lined up with the tumour can also be used[26,27,49]. This technique militates against extra-axillary node identification but is easy and efficient[50–52]. Using a combination of radioisotope and blue dye, the SLN was identified successfully in 98% of cases with no false negative results[53]. Subareolar injection of blue dye alone has been shown to demonstrate a sentinel lymph node in 98% of cases with no false negative sentinel nodes[50,54]. Likewise, it has been shown that subareolar injection of technetium is equivalent to peritumoural injection of blue dye[55,56]. One centre uses the combined intraparenchymal and subdermal injection technique because it more accurately reflects all lymphatic flow from breast tumour[38]. Intraparenchymal injections consistently visualise a more diverse pattern of lymph flow. In particular, the internal mammary chains and supraclavicular nodes are commonly seen after intraparenchymal injection but rarely after subareolar or subdermal injections. Peritumoural and subdermal injection of ^{99m}Tc sulphur colloid combined with periareolar injection of isosulphan blue dye is advocated by another group with extensive experience[32,57–59]. Overall, the identification rate, accuracy and predictive value of sentinel node biopsy seem to be unaffected by the site of injection though a difference may become apparent with long-term follow-up that examines the pattern of axillary failure correlated with the injection site[13].

When should injection be performed?

Comparable accuracies have been shown for same day and day before surgery radioisotope injections[60,61]. After injection breast massage may be performed to augment lymphatic flow[62]. However, concern exists that tumour cells might be transported from the primary tumour into the lymphatics. Pressure within the lymphatics can increase up to 22-fold following external massage and transport of tumour cells to the lymphatic spaces has been demonstrated[63–65]. However, isolated tumour cells are not true metastases and do not have malignant potential. Intraoperative injection is little used as it requires transfer of radioisotope to the operating theatre, is not as reliable and is complicated by radiation safety issues.

Pathology

The role of the pathology laboratory is pivotal to the success of the procedure. In particular the development of multisectioning and immunohistochemistry (IHC) staining techniques has been reported to increase the rate of detection of malignant disease by up to 33%[66–68]. IHC can be particularly beneficial in patients with invasive lobular cancer[69,70]. Trials currently in progress aim to determine the significance of IHC detected micrometastases in patients treated by conventional pathological criteria[71]. It has been shown recently that patients with favourable breast cancer histology have only a small risk of axillary sentinel lymph node metastases and that biopsy is not necessary in all these patients[72].

Radiation safety

Several papers have discussed various aspects of radiation safety associated with the sentinel node in detail[73–78]. Radiation doses are low and no additional procedures are required for the protection of staff. The procedure can be performed safely during pregnancy as the foetal dose is very low.

Clinical issues

The procedure is not contraindicated in patients with clinically palpable axillary nodes[18]. Relative contraindications include prior axillary surgery and subglandular breast implants. In one centre, more than 50 patients with subpectoral implants have been associated with 100% SLN identification success rate and no clinically detected recurrences in patients with negative SLN biopsy[8]. For patients with a primary tumour greater than 4 cm, the success of SLNB shows little difference to those with smaller tumours[12]. In patients with multifocal breast cancer, sentinel node identification has been reported in 94% and is an accurate predictor of nodal status[79]. This type of cancer favours a periareolar or subareolar injection protocol. SLNB performed following excisional biopsy demonstrates satisfactory results[29,80]. Patients with ductal carcinoma-*in-situ* (DCIS) have an excellent long term prognosis (98% survival) but 10%–29% of these patients will have invasive cancer at definitive surgery[81–87]. Analysis of resected nodes from patients who had negative axillary surgery previously, demonstrated micrometastases in 13% of nodes but none in patients who had disease recurrence[88]. This would indicate that SNLB is not necessary in these patients.

False negative rate

The false negative rate is the percentage of node positive patients who are missed by mapping[8]. In one centre there has been no axillary recurrence (mean 5 years) following a negative node biopsy in 1914 patients[8]. Data from case control studies to date indicate SLN biopsy to be highly predictive of axillary node status with a false negative rate of less than 5%[89]. Reasons for false negative results are attributed to changes in surgical personnel, difficult lymph node location and absence of a thorough histological study[90]. Factors militating against sentinel node identification are increasing age and body mass index[91]. A review of ten large observational studies revealed just ten axillary recurrences in 2664 patients (0.4%) who did not undergo ALND following negative SLN biopsy[43]. A large recent study comprising 4008 patients and a median follow-up of 31 months had an overall axillary recurrence rate of 0.25%[92]. A further study in 234 patients (median follow-up 42 months) did not find an increased rate of axillary recurrence in patients with negative SLN or SLN micrometastases[93]. As the axillary recurrence rate should not exceed that seen after conventional axillary clearance surgery (1.0%–2.3%), the figures quoted above compare very favourably[94–96].

Internal mammary and intramammary lymph nodes

Intramammary nodes with metastases have been documented as independent predictors of poor outcome for patients with breast cancer[97]. In one centre analysing the results of 640 patients, 94% demonstrated a sentinel node in the ipsilateral axilla and 46% also had sentinel nodes outside the axilla[34]. In 5% of patients drainage was exclusively to non-axillary sentinel nodes. The most important non-axillary drainage was to the internal mammary nodal chain and 40% of patients demonstrated a sentinel node in this area[34]. Sentinel lymph node biopsy of internal mammary nodes is associated with a low morbidity and has been shown to improve staging and change treatment strategy[98,99]. Proponents of evaluating internal mammary nodes argue that this supports lymphatic mapping as it provides more accurate staging although its impact on outcome is less clear[100,101]. Nonetheless, it has been demonstrated that metastases in the internal mammary nodes influence survival in a manner comparable to that of metastases in axillary lymph nodes[102]. A review with 30 years of results demonstrated that patients with isolated IMN disease have a prognosis equivalent to that of patients with isolated axillary metastases[103]. A combination of metastatic disease in both axillary and internal mammary nodal chains has an especially poor prognosis with a 10-year survival of 37%[104]. Internal mammary nodes identified on preoperative lymphoscintigraphy require histopathological confirmation of disease before therapy is commenced[105]. Internal mammary nodes are best identified when peritumoural, intratumoural or subtumoural injections are made with some reports visualising these nodes in 10%–30% of patients whereas subdermal, intradermal, periareolar or subareolar injections result in much less frequent visualisation of these nodes[47,58].

Micrometastases

Micrometastases are defined as tumour deposits in nodes ranging from 0.2 to 2 mm with cells less than 0.2 mm known as isolated tumour cells[106]. Despite the evidence of some retrospective studies there is controversy regarding the prognostic significance of micrometastases found only by immunohistochemistry staining, particularly when only isolated tumour cells are found[71]. A literature review on the clinical significance of micrometastases concluded that they were associated with a poorer prognosis than that associated with no axillary involvement[107]. In a study involving a 15-year

follow-up on almost 100 patients and 1539 axillary lymph nodes with pT1 breast cancer determined that half of the patients developed distant metastases[108]. However, recent studies involving 234 patients and 84 patients (median follow-up 42 and 40 months, respectively) showed that micrometastases were not associated with an increased risk of axillary recurrence or that outcome was significantly affected by the presence of micrometastases[93,109]. Micrometastases are not reliably detected by FDG-PET imaging[110,111].

Neoadjuvant therapy

In published work to date the SLN identification rate has ranged from 84% to 97% implying that the accuracy of sentinel node biopsy is not influenced by neoadjuvant therapy[112–121]. Questions remain as to whether all nodes respond equally to therapy and a high false negative rate (up to 33%) has been reported in some of these series. Pending further clarification, it is still probably best to perform SLNB prior to commencement of neoadjuvant therapy.

Summary

Lymphatic mapping for breast cancer is rapidly becoming the standard of care but there is no single study that demonstrates conclusively which particular sentinel node protocol is best for a specific patient. The results from three multicentre trials sponsored by the National Cancer Institute (due to report in 2007) attempting to answer some of the issues discussed above are eagerly awaited.

References

[1] Fisher ER, Costantino J, Fisher B, Redmond C. Pathologic findings from the National Surgical Adjuvant Breast Project (Protocol 4). Discriminants for 15-year survival. National Surgical Adjuvant Breast and Bowel Project Investigators. Cancer 1993; 71: 2141–50.

[2] Fitzgibbons PL, Page DL, Weaver D *et al*. Prognostic factors in breast cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 2000; 124: 966–78.

[3] Singletary SE, Allred C, Ashley P *et al*. Revision of the American Joint Committee on Cancer staging system for breast cancer. J Clin Oncol 2002; 20: 3628–36.

[4] Warmuth MA, Bowen G, Prosnitz LR *et al*. Complications of axillary lymph node dissection for carcinoma of the breast: a report based on a patient survey. Cancer 1998; 83: 1362–8.

[5] Hack TF, Cohen L, Katz J, Robson LS, Goss P. Physical and psychological morbidity after axillary lymph node dissection for breast cancer. J Clin Oncol 1999; 17: 143–9.

[6] Schrenk P, Rieger R, Shamiyeh A, Wayand W. Morbidity following sentinel lymph node biopsy versus axillary lymph node dissection for patients with breast carcinoma. Cancer 2000; 88: 608–14.

[7] Morton DL, Bostick PJ. Will the true sentinel node please stand? Ann Surg Oncol 1999; 6: 12–4.

[8] Jakub JW, Cox CE, Pippas AW, Gardner M, Pendas S, Reintgen DS. Controversial topics in breast lymphatic mapping. Semin Oncol 2004; 31: 324–32.

[9] Kapteijn BA, Nieweg OE, Petersen JL *et al*. Identification and biopsy of the sentinel lymph node in breast cancer. Eur J Surg Oncol 1998; 24: 427–30.

[10] McMasters KM, Wong SL, Chao C *et al*. Defining the optimal surgeon experience for breast cancer sentinel lymph node biopsy: a model for implementation of new surgical techniques. Ann Surg 2001; 234: 292–9; discussion 299–300.

[11] Krag DN, Harlow S. Current status of sentinel node surgery in breast cancer. Oncology (Williston Park) 2003; 17: 1663–6; discussion 1669–70, 1675–6.

[12] Jakub JW, Pendas S, Reintgen DS. Current status of sentinel lymph node mapping and biopsy: facts and controversies. Oncologist 2003; 8: 59–68.

[13] Chao C, Wong SL, Tuttle TM *et al*. Sentinel lymph node biopsy for breast cancer: improvement in results over time. Breast J 2004; 10: 337–44.

[14] Giuliano AE, Jones RC, Brennan M, Statman R. Sentinel lymphadenectomy in breast cancer. J Clin Oncol 1997; 15: 2345–50.

[15] Krag D, Weaver D, Ashikaga T *et al*. The sentinel node in breast cancer – a multicentervalidation study. N Engl J Med 1998; 339: 941–6.

[16] Borgstein PJ, Pijpers R, Comans EF, van Diest PJ, Boom RP, Meijer S. Sentinel lymph node biopsy in breast cancer: guidelines and pitfalls of lymphoscintigraphy and gamma probe detection. J Am Coll Surg 1998; 186: 275–83.

[17] Liberman L, Cody HS 3rd, Hill AD *et al*. Sentinel lymph node biopsy after percutaneous diagnosis of nonpalpable breast cancer. Radiology 1999; 211: 835–44.

[18] Specht MC, Fey JV, Borgen PI, Cody HS 3rd. Is the clinically positive axilla in breast cancer really a contraindication to sentinel lymph node biopsy? J Am Coll Surg 2005; 200: 10–4.

[19] Edreira MM, Colombo LL, Perez JH, Sajaroff EO, de Castiglia SG. In vivo evaluation of three different 99mTc-labelled radiopharmaceuticals for sentinel lymph node identification. Nucl Med Commun 2001; 22: 499–504.

[20] Derossis AM, Fey J, Yeung H *et al*. A trend analysis of the relative value of blue dye and isotope localization in 2,000 consecutive cases of sentinel node biopsy for breast cancer. J Am Coll Surg 2001; 193: 473–8.

[21] Radovanovic Z, Golubovic A, Plzak A, Stojiljkovic B, Radovanovic D. Blue dye versus combined blue dye-radioactive tracer technique in detection of sentinel lymph node in breast cancer. Eur J Surg Oncol 2004; 30: 913–7.

[22] Pelosi E, Ala A, Bello M *et al*. Impact of axillary nodal metastases on lymphatic mapping and sentinel lymph node identification rate in patients with early stage breast cancer. Eur J Nucl Med Mol Imaging 2005; Epub ahead of print.

[23] Mariani G, Moresco L, Viale G *et al*. Radioguided sentinel lymph node biopsy in breast cancer surgery. J Nucl Med 2001; 42: 1198–215.

[24] Motomura K, Noguchi A, Hashizume T *et al*. Usefulness of a solid-state gamma camera for sentinel node identification in patients with breast cancer. J Surg Oncol 2005; 89: 12–7.

[25] Borgstein PJ, Meijer S, Pijpers RJ, van Diest PJ. Functional lymphatic anatomy for sentinel node biopsy in breast cancer: echoes from the past and the periareolar blue method. Ann Surg 2000; 232: 81–9.

[26] Pelosi E, Baiocco C, Ala A *et al*. Lymphatic mapping in early stage breast cancer: comparison between periareolar and subdermal injection. Nucl Med Commun 2003; 24: 519–23.

[27] Pelosi E, Bello M, Giors M *et al*. Sentinel lymph node detection in patients with early-stage breast cancer: comparison of periareolar and subdermal/peritumoral injection techniques. J Nucl Med 2004; 45: 220–5.

[28] Wong SL, Edwards MJ, Chao C *et al*. Sentinel lymph node biopsy for breast cancer: impact of the number of sentinel nodes removed on the false-negative rate. J Am Coll Surg 2001; 192: 684–9; discussion 689–91.

[29] Pendas S, Giuliano R, Swor G, Gardner M, Jakub J, Reintgen DS. Worldwide experience with lymphatic mapping for invasive breast cancer. Semin Oncol 2004; 31: 318–23.

[30] Torrenga H, Meijer S, Fabry H, van der Sijp J. Sentinel node biopsy in breast cancer patients: triple technique as a routine procedure. Ann Surg Oncol 2004; 11: S231–5.

[31] Cox CE, Salud CJ, Cantor A *et al*. Learning curves for breast cancer sentinel lymph node mapping based on surgical volume analysis. J Am Coll Surg 2001; 193: 593–600.

[32] Aarsvold JN, Alazraki NP. Update on detection of sentinel lymph nodes in patients with breast cancer. Semin Nucl Med 2005; 35: 116–28.

[33] Uren RF, Thompson JF, Howman-Giles R. Lymphatic drainage of the skin and breast: locating the sentinel nodes, Amsterdam: Harwood Academic, 1999.

[34] Uren RF, Howman-Giles R, Chung D, Thompson JF. Nuclear medicine aspects of melanoma and breast lymphatic mapping. Semin Oncol 2004; 31: 338–48.

[35] Tanis PJ, Nieweg OE, Valdes Olmos RA, Kroon BB. Anatomy and physiology of lymphatic drainage of the breast from the perspective of sentinel node biopsy. J Am Coll Surg 2001; 192: 399–409.

[36] Turner-Warwick RT. The lymphatics of the breast. Br J Surg 1959; 46: 574–82.

[37] Shen P, Glass EC, DiFronzo LA, Giuliano AE. Dermal versus intraparenchymal lymphoscintigraphy of the breast. Ann Surg Oncol 2001; 8: 241–8.

[38] Kaleya RN, Heckman JT, Most M, Zager JS. Lymphatic mapping and sentinel node biopsy: a surgical perspective. Semin Nucl Med 2005; 35: 129–34.

[39] Nieweg OE, Jansen L, Valdes Olmos RA *et al*. Lymphatic mapping and sentinel lymph node biopsy in breast cancer. Eur J Nucl Med 1999; 26: S11–6.

[40] Canavese G, Gipponi M, Catturich A *et al*. Pattern of lymphatic drainage to the sentinel lymph node in breast cancer patients. J Surg Oncol 2000; 74: 69–74.

[41] Byrd DR, Dunnwald LK, Mankoff DA *et al*. Internal mammary lymph node drainage patterns in patients with breast cancer documented by breast lymphoscintigraphy. Ann Surg Oncol 2001; 8: 234–40.

[42] Estourgie SH, Nieweg OE, Olmos RA, Rutgers EJ, Kroon BB. Lymphatic drainage patterns from the breast. Ann Surg 2004; 239: 232–7.

[43] Nieweg OE, Estourgie SH, van Rijk MC, Kroon BB. Rationale for superficial injection techniques in lymphatic mapping in breast cancer patients. J Surg Oncol 2004; 87: 153–6.

[44] Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy forbreast cancer. Ann Surg 1994; 220: 391–8; discussion 398–401.

[45] Albertini JJ, Lyman GH, Cox C *et al*. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. JAMA 1996; 276: 1818–22.

[46] Lin KM, Patel TH, Ray A *et al*. Intradermal radioisotope is superior to peritumoral blue dye or radioisotope in identifying breast cancer sentinel nodes. J Am Coll Surg 2004; 199: 561–6.

[47] Park C, Seid P, Morita E *et al*. Internal mammary sentinel lymph node mapping for invasive breast cancer: implications for staging and treatment. Breast J 2005; 11: 29–33.

[48] Borgstein PJ, Meijer S, Pijpers R. Intradermal blue dye to identify sentinel lymph-node in breast cancer. Lancet 1997; 349: 1668–9.

[49] Krynyckyi BR, Kim CK, Mosci K *et al*. Areolar-cutaneous 'junction injections' to augment sentinel node count activity. Clin Nucl Med 2003; 28: 97–107.

[50] Kern KA. Lymphoscintigraphic anatomy of sentinel lymphatic channels after subareolar injection of Technetium 99m sulfur colloid. J Am Coll Surg 2001; 193: 601–8.

[51] Kern KA. Breast lymphatic mapping using subareolar injections of blue dye and radiocolloid: illustrated technique. J Am Coll Surg 2001; 192: 545–50.

[52] Vargas HI, Tolmos J, Agbunag RV *et al*. A validation trial of subdermal injection compared with intraparenchymal injection for sentinel lymph node biopsy in breast cancer. Am Surg 2002; 68: 87–91.

[53] Kern KA. Concordance and validation study of sentinel lymph node biopsy for breast cancer using subareolar injection of blue dye and technetium 99m sulfur colloid. J Am Coll Surg 2002; 195: 467–75.

[54] Kern KA. Sentinel lymph node mapping in breast cancer using subareolar injection of blue dye. J Am Coll Surg 1999; 189: 539–45.

[55] Klimberg VS, Rubio IT, Henry R, Cowan C, Colvert M, Korourian S. Subareolar versus peritumoral injection for location of the sentinel lymph node. Ann Surg 1999; 229: 860–4; discussion 864–5.

[56] Chagpar A, Martin RC 3rd, Chao C *et al*. Validation of subareolar and periareolar injection techniques for breast sentinel lymph node biopsy. Arch Surg 2004; 139: 614–8; discussion 618–20.

[57] Alazraki NP, Styblo T, Grant SF, Cohen C, Larsen T, Aarsvold JN. Sentinel node staging of early breast cancer using lymphoscintigraphy and the intraoperative gamma-detecting probe. Semin Nucl Med 2000; 30: 56–64.

[58] Alazraki NP, Styblo T, Grant SF *et al*. Sentinel node staging of early breast cancer using lymphoscintigraphy and the intraoperative gamma detecting probe. Radiol Clin North Am 2001; 39: 947–56, viii.

[59] Styblo T, Aarsvold JN, Grant SF *et al*. Sentinel lymph

nodes: optimizing success. Semin Roentgenol 2001; 36: 261–9.

[60] McCarter MD, Yeung H, Yeh S, Fey J, Borgen PI, Cody HS 3rd. Localization of the sentinel node in breast cancer: identical results with same-day and day-before isotope injection. Ann Surg Oncol 2001; 8: 682–6.

[61] Babiera GV, Delpassand ES, Breslin TM *et al*. Lymphatic drainage patterns on early versus delayed breast lymphoscintigraphy performed after injection of filtered Tc-99m sulfur colloid in breast cancer patients undergoing sentinel lymph node biopsy. Clin Nucl Med 2005; 30: 11–5.

[62] Bass SS, Cox CE, Salud CJ *et al*. The effects of postinjection massage on the sensitivity of lymphatic mapping in breast cancer. J Am Coll Surg 2001; 192: 9–16.

[63] Ikomi F, Hunt J, Hanna G, Schmid-Schonbein GW. Interstitial fluid, plasma protein, colloid, and leukocyte uptake into initial lymphatics. J Appl Physiol 1996; 81: 2060–7.

[64] Carter BA, Jensen RA, Simpson JF, Page DL. Benign transport of breast epithelium into axillary lymph nodes after biopsy. Am J Clin Pathol 2000; 113: 259–65.

[65] Diaz NM, Cox CE, Ebert M *et al*. Benign mechanical transport of breast epithelial cells to sentinel lymph nodes. Am J Surg Pathol 2004; 28: 1641–5.

[66] Dowlatshahi K, Fan M, Snider HC, Habib FA. Lymph node micrometastases from breast carcinoma: reviewing the dilemma. Cancer 1997; 80: 1188–97.

[67] Turner RR, Chu KU, Qi K *et al*. Pathologic features associated with nonsentinel lymph node metastases in patients with metastatic breast carcinoma in a sentinel lymph node. Cancer 2000; 89: 574–81.

[68] Cohen C, Alazraki N, Styblo T, Waldrop SM, Grant SF, Larsen T. Immunohistochemical evaluation of sentinel lymph nodes in breast carcinoma patients. Appl Immunohistochem Mol Morphol 2002; 10: 296–303.

[69] Trojani M, de Mascarel I, Coindre JM, Bonichon F. Micrometastases to axillary lymph nodes from invasive lobular carcinoma of breast: detection by immunohistochemistry and prognostic significance. Br J Cancer 1987; 56: 838–9.

[70] Cote RJ, Peterson HF, Chaiwun B *et al*. Role of immunohistochemical detection of lymph-node metastases in management of breast cancer. International Breast Cancer Study Group. Lancet 1999; 354: 896–900.

[71] Quan ML, Cody HS 3rd. Missed micrometastatic disease in breast cancer. Semin Oncol 2004; 31: 311–7.

[72] Mendez JE, Fey JV, Cody H, Borgen PI, Sclafani LM. Can sentinel lymph node biopsy be omitted in patients with favorable breast cancer histology? Ann Surg Oncol 2005; 12: 24–8.

[73] Fitzgibbons PL, LiVolsi VA. Recommendations for handling radioactive specimens obtained by sentinel lymphadenectomy. Surgical Pathology Committee of the College of American Pathologists, and the Association of Directors of Anatomic and Surgical Pathology. Am J Surg Pathol 2000; 24: 1549–51.

[74] Nugent N, Hill AD, Casey M *et al*. Safety guidelines for radiolocalised sentinel node resection. Ir J Med Sci 2001; 170: 236–8.

[75] Morton R, Horton PW, Peet DJ, Kissin MW. Quantitative assessment of the radiation hazards and risks in sentinel node procedures. Br J Radiol 2003; 76: 117–22.

[76] Gentilini O, Cremonesi M, Trifiro G *et al*. Safety of sentinel node biopsy in pregnant patients with breast cancer. Ann Oncol 2004; 15: 1348–51.

[77] Michel R, Hofer C. Radiation safety precautions for sentinel lymph node procedures. Health Phys 2004; 86: S35–7.

[78] Law M, Chow LW, Kwong A, Lam CK. Sentinel lymph node technique for breast cancer: radiation safety issues. Semin Oncol 2004; 31: 298–303.

[79] Tousimis E, Van Zee KJ, Fey JV *et al*. The accuracy of sentinel lymph node biopsy in multicentric and multifocal invasive breast cancers. J Am Coll Surg 2003; 197: 529–35.

[80] Haigh PI, Hansen NM, Qi K, Giuliano AE. Biopsy method and excision volume do not affect success rate of subsequent sentinel lymph node dissection in breast cancer. Ann Surg Oncol 2000; 7: 21–7.

[81] Cox CE, Nguyen K, Gray RJ *et al*. Importance of lymphatic mapping in ductal carcinoma *in situ* (DCIS): why map DCIS? Am Surg 2001; 67: 513–9; discussion 519–21.

[82] Burak WE Jr, Owens KE, Tighe MB *et al*. Vacuum-assisted stereotactic breast biopsy: histologic underestimation of malignant lesions. Arch Surg 2000; 135: 700–3.

[83] Lee CH, Carter D, Philpotts LE *et al*. Ductal carcinoma *in situ* diagnosed with stereotactic core needle biopsy: can invasion be predicted? Radiology 2000; 217: 466–70.

[84] Klauber-DeMore N, Tan LK, Liberman L *et al*. Sentinel lymph node biopsy: is it indicated in patients with high-risk ductal carcinoma-*in-situ* and ductal carcinoma-*in-situ* with microinvasion? Ann Surg Oncol 2000; 7: 636–42.

[85] Darling ML, Smith DN, Lester SC *et al*. Atypical ductal hyperplasia and ductal carcinoma *in situ* as revealed by large-core needle breast biopsy: results of surgical excision. AJR Am J Roentgenol 2000; 175: 1341–6.

[86] Renshaw AA. Predicting invasion in the excision specimen from breast core needle biopsy specimens with only ductal carcinoma *in situ*. Arch Pathol Lab Med 2002; 126: 39–41.

[87] Mendez I, Andreu FJ, Saez E *et al*. Ductal carcinoma *in situ* and atypical ductal hyperplasia of the breast diagnosed at stereotactic core biopsy. Breast J 2001; 7: 14–8.

[88] Lara JF, Young SM, Velilla RE, Santoro EJ, Templeton SF. The relevance of occult axillary micrometastasis in ductal carcinoma *in situ*: a clinicopathologic study with long-term follow-up. Cancer 2003; 98: 2105–13.

[89] Mansel RE, Goyal A. European studies on breast lymphatic mapping. Semin Oncol 2004; 31: 304–10.

[90] Vidal-Sicart S, Pons F, Puig S *et al*. Identification of the sentinel lymph node in patients with malignant melanoma: what are the reasons for mistakes? Eur J Nucl Med Mol Imaging 2003; 30: 362–6.

[91] Cox CE, Dupont E, Whitehead GF *et al*. Age and body mass index may increase the chance of failure in sentinel lymph node biopsy for women with breast cancer. Breast J 2002; 8: 88–91.

[92] Naik AM, Fey J, Gemignani M *et al*. The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection:

a follow-up study of 4008 procedures. Ann Surg 2004; 240: 462–8; discussion 468–71.
[93] Langer I, Marti WR, Guller U *et al*. Axillary recurrence rate in breast cancer patients with negative sentinel lymph node (SLN) or SLN micrometastases: prospective analysis of 150 patients after SLN biopsy. Ann Surg 2005; 241: 152–8.
[94] Recht A, Pierce SM, Abner A *et al*. Regional nodal failure after conservative surgery and radiotherapy for early-stage breast carcinoma. J Clin Oncol 1991; 9: 988–96.
[95] Fredriksson I, Liljegren G, Arnesson LG *et al*. Consequences of axillary recurrence after conservative breast surgery. Br J Surg 2002; 89: 902–8.
[96] Nieweg OE, van Rijk MC, Valdes Olmos RA, Hoefnagel CA. Sentinel node biopsy and selective lymph node clearance-impact on regional control and survival in breast cancer and melanoma. Eur J Nucl Med Mol Imaging 2005; 32: 631–4.
[97] Shen J, Hunt KK, Mirza NQ *et al*. Intramammary lymph node metastases are an independent predictor of poor outcome in patients with breast carcinoma. Cancer 2004; 101: 1330–7.
[98] Tanis PJ, Nieweg OE, Valdes Olmos RA *et al*. Impact of non-axillary sentinel node biopsy on staging and treatment of breast cancer patients. Br J Cancer 2002; 87: 705–10.
[99] Noguchi M. Relevance and practicability of internal mammary sentinel node biopsy for breast cancer. Breast Cancer 2002; 9: 329–36.
[100] Galimberti V, Veronesi P, Arnone P *et al*. Stage migration after biopsy of internal mammary chain lymph nodes in breast cancer patients. Ann Surg Oncol 2002; 9: 924–8.
[101] Fabry HF, Mutsaers PG, Meijer S *et al*. Clinical relevance of parasternal uptake in sentinel node procedure for breast cancer. J Surg Oncol 2004; 87: 13–8.
[102] Bevilacqua JL, Gucciardo G, Cody HS *et al*. A selection algorithm for internal mammary sentinel lymph node biopsy in breast cancer. Eur J Surg Oncol 2002; 28: 603–14.
[103] Veronesi U, Marubini E, Mariani L, Valagussa P, Zucali R. The dissection of internal mammary nodes does not improve the survival of breast cancer patients. 30-year results of a randomised trial. Eur J Cancer 1999; 35: 1320–5.
[104] Veronesi U, Cascinelli N, Bufalino R *et al*. Risk of internal mammary lymph node metastases and its relevance on prognosis of breast cancer patients. Ann Surg 1983; 198: 681–4.
[105] Benda RK, Cendan JC, Copeland EM *et al*. Should decisions on internal mammary lymph node irradiation be based on current lymphoscintigraphy techniques for sentinel lymph node identification? Cancer 2004; 100: 518–23.
[106] Hermanek P, Hutter RV, Sobin LH, Wittekind C. International Union Against Cancer. Classification of isolated tumor cells and micrometastasis. Cancer 1999; 86: 2668–73.
[107] Sakorafas GH, Geraghty J, Pavlakis G. The clinical significance of axillary lymph node micrometastases in breast cancer. Eur J Surg Oncol 2004; 30: 807–16.
[108] Susnik B, Frkovic-Grazio S, Bracko M. Occult micrometastases in axillary lymph nodes predict subsequent distant metastases in stage I breast cancer: a case-control study with 15-year follow-up. Ann Surg Oncol 2004; 11: 568–72.
[109] Chagpar A, Middleton LP, Sahin AA *et al*. Clinical outcome of patients with lymph node-negative breast carcinoma who have sentinel lymph node micrometastases detected by immunohistochemistry. Cancer 2005; 103: 1581–6.
[110] Lovrics PJ, Chen V, Coates G *et al*. A prospective evaluation of positron emission tomography scanning, sentinel lymph node biopsy, and standard axillary dissection for axillary staging in patients with early stage breast cancer. Ann Surg Oncol 2004; 11: 846–53.
[111] Zornoza G, Garcia-Velloso MJ, Sola J, Regueira FM, Pina L, Beorlegui C. 18F-FDG PET complemented with sentinel lymph node biopsy in the detection of axillary involvement in breast cancer. Eur J Surg Oncol 2004; 30: 15–9.
[112] Breslin TM, Cohen L, Sahin A *et al*. Sentinel lymph node biopsy is accurate after neoadjuvant chemotherapy for breast cancer. J Clin Oncol 2000; 18: 3480–6.
[113] Fernandez A, Cortes M, Benito E *et al*. Gamma probe sentinel node localization and biopsy in breast cancer patients treated with a neoadjuvant chemotherapy scheme. Nucl Med Commun 2001; 22: 361–6.
[114] Haid A, Tausch C, Lang A *et al*. Is sentinel lymph node biopsy reliable and indicated after preoperative chemotherapy in patients with breast carcinoma? Cancer 2001; 92: 1080–4.
[115] Brady EW. Sentinel lymph node mapping following neoadjuvant chemotherapy for breast cancer. Breast J 2002; 8: 97–100.
[116] Stearns V, Ewing CA, Slack R, Penannen MF, Hayes DF, Tsangaris TN. Sentinel lymphadenectomy after neoadjuvant chemotherapy for breast cancer may reliably represent the axilla except for inflammatory breast cancer. Ann Surg Oncol 2002; 9: 235–42.
[117] Miller AR, Thomason VE, Yeh IT *et al*. Analysis of sentinel lymph node mapping with immediate pathologic review in patients receiving preoperative chemotherapy for breast carcinoma. Ann Surg Oncol 2002; 9: 243–7.
[118] Julian TB, Dusi D, Wolmark N. Sentinel node biopsy after neoadjuvant chemotherapy for breast cancer. Am J Surg 2002; 184: 315–7.
[119] Piato JR, Barros AC, Pincerato KM, Sampaio AP, Pinotti JA. Sentinel lymph node biopsy in breast cancer after neoadjuvant chemotherapy. A pilot study. Eur J Surg Oncol 2003; 29: 118–20.
[120] Patel NA, Piper G, Patel JA, Malay MB, Julian TB. Accurate axillary nodal staging can be achieved after neoadjuvant therapy for locally advanced breast cancer. Am Surg 2004; 70: 696–9; discussion 699–700.
[121] Mamounas EP, Brown A, Anderson S *et al*. Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2005; 23: 2694–702.

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Screening women at increased risk with MRI

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Abstract

Breast cancer is the most common cancer affecting women. In the screening of women for breast cancer, mammography is the most used imaging modality. Women with an increased risk for getting breast cancer can develop a malignancy at a relatively young age compared to other women. The increased risk for developing breast cancer can usually be found in a positive familial history. This positive familial history is based on a gene mutation in 5–10% of cases. The most common gene mutations are $BRCA_1$ and $BRCA_2$. This risk makes it necessary to start screening these women at a young age. Mammography, however, has proven to be less reliable in younger women because its sensitivity is lowered due to the dense breast tissue often present in this group. MRI has a higher sensitivity for detecting breast cancer compared to mammography. MRI is not influenced by the density of the breast tissue. This makes breast MRI the best modality available for the screening of women with an increased risk for developing breast cancer.

Keywords: *Breast; cancer; screening; high risk.*

Introduction

Breast cancer is the most common cancer affecting women and has an enormous impact on their health. The incidence of breast cancer varies between countries with the highest incidence in the United States and Northern Europe. In the United States breast cancer makes up 30% of all cancers in women, while in The Netherlands the lifetime risk for a woman for developing breast cancer is about 11%[1].

The aetiology of breast cancer is varied: inherited genetic susceptibility, acquired genetic changes, and effects of endogenous and exogenous environment factors. The interactions of all these factors contribute to the development of breast cancer.

There is limited and indirect evidence that self-examination and physical examination can help in decreasing mortality because tumours smaller than 10 mm will not be detected in the majority of the cases[2].

Most breast cancers are detected with mammography in either a screening situation or by the discovery of a palpable breast mass. The smaller the tumour is at detection, the better the prognosis[3].

Randomised trials have shown that screening with mammography in the age category of 50–70 years can reduce mortality by about 25%. However, there is no consensus at the moment about the value of screening younger women with mammography. One of the reasons is the lower sensitivity of mammography in women below the age of 50 years. This is because young, pre-menopausal, women have denser breasts compared to post-menopausal women, resulting in an increased chanced that a malignancy will be missed on mammography[4].

In a diagnostic setting, magnetic resonance imaging (MRI) is a very sensitive tool for the detection of breast cancer. Especially for invasive breast cancer, the sensitivity of this imaging technique is reported to be above 95%[5]. This sensitivity is not influenced in any way by the amount of glandular tissue present in the breast. However the specificity of this modality is only moderate. The role of MRI as a screening modality has not yet been outlined. In the literature, MRI has only been evaluated as a screening tool for women with an increased risk for developing breast cancer[6–8]. In this paper the role of MRI in the screening of women with an increased risk for developing breast cancer is discussed.

Increased risk for breast cancer

There are two categories of women who have an increased risk for developing breast cancer.

The first group are those with a family history of breast cancer. Approximately 20%–30% of women with breast cancer have a positive family history and about 20% of these individuals have a first degree relative with breast cancer[9]. Only about 5%–10% of all cases of breast cancer are caused by inherited factors. The most common gene mutations are the $BRCA_1$ and $BRCA_2$.

In 1990, Hall and co-workers identified chromosome 17 q 21 as the location of a susceptibility gene for early onset breast cancer, now known as the $BRCA_1$ gene mutation[10]. Shortly after that Narod[11] described a linkage between the genetic marker D17 S 74 on 17 q 21 and ovarian cancer. In two different studies the suggestion has been made that about 3% of all breast cancers are caused by the $BRCA_1$ gene[12,13] and about 45% of all hereditary cases of breast cancer are caused by the $BRCA_1$ mutation. Mutations in the $BRCA_1$ are most commonly seen in Russia, followed by Israel and Italy[14]. Women who are carriers of the $BRCA_1$ gene mutation have a lifetime risk (LTR) for developing breast cancer of approximately 80%. Exogenous hormone and carcinogen exposure are also risk-modifying factors in this group.

Other malignancies suggested to have an increased prevalence in these families are ovarian cancer, prostate and colonic cancer[12]. $BRCA_1$ associated breast malignancies tend to have a high malignancy grade and are often oestrogen and progesterone receptor negative. The tumour is also highly proliferative[15]. Median age of onset of breast cancer in this group is younger than 45 years[16].

Approximately 35% of all inherited breast cancers are caused by the $BRCA_2$ mutation, first identified by Wooster *et al.*[17]. They also described a linkage between $BRCA_2$ mutation and male breast cancer. The estimated LTR for developing breast cancer in this group is somewhat lower than in the $BRCA_1$ group. It has been suggested by Ursin[18] that in this group the use of oral contraceptives also increases the risk for developing breast cancer.

A variety of other malignancies are associated with the $BRCA_2$ carriers. Non-Hodgkin's lymphoma has been reported and also prostate cancer and bladder cancer[19,20]. The $BRCA_2$ mutation is associated with a 6% LTR of male breast cancer[21], which means a 100-fold increase over the general male population. At the moment little is known about the malignancy grade and receptor status in the $BRCA_2$ group[15].

For both the $BRCA_1$ and $BRCA_2$ mutation carriers, the LTR for a contralateral breast cancer is about 65%[15].

There are other more sporadic hereditary diseases with an increased risk for developing breast cancer. The Li–Fraumeni syndrome was first identified in 1969[22]. It is an autosomal dominant disease causing an increased risk for developing among others breast cancer, different types of sarcoma and leukaemia. In this group 30% of all malignancies occur before the age of 15. Cowden's disease or multiple hamartoma syndrome showed an increased risk for both benign breast disorders like fibroadenomas and nipple malformations and breast malignancies[23,24]. Other hereditary diseases such as ataxia telangiectasia and the Peutz–Jeghers syndrome (hamartomous polyps in the small bowel) and the Muir–Torre syndrome (a variant of hereditary non-polyposis colon cancer) also give an increased risk for breast cancer[25].

Another group of women with an increased risk for breast cancer consists of women who have an individual risk factor. Patients with a history of lobular carcinoma *in situ* (LCIS) have a somewhat increased incidence of developing an invasive cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABBP) suggested an incidence of 13 invasive malignancies in 1000 women with an LCIS[26]. In this group there is also a risk for bilateral breast cancer. Ductal carcinoma *in situ* (DCIS) also gives an increased risk for an invasive breast malignancy. About 30% of women not treated postoperatively with irradiation developed an invasive malignancy after a mean interval of 6 years[27,28]. Invasive lobular carcinoma is characterized by multifocality in the ipsilateral breast and appears to be more often bilateral[29] than other types of invasive malignancies[30].

In the updated results of the nurses' Health Study, post- or per-menopausal use of hormones showed an excess risk for developing breast cancer in the group of women with current or recently used hormones[31]. The risk increased with increasing duration.

Women treated with irradiation of the chest for, for instance, (non-)Hodgkin's lymphoma, also have an increased risk for developing breast cancer. The excess risk in this category of patients is dependent on dose and age at irradiation. The younger the age at time of exposure to irradiation, the younger the onset of breast cancer[32].

Screening of the breast

Currently there are four possible breast screening modalities: clinical examination, mammography, ultrasound and MRI. The primary goal of breast examinations during screening is the detection of breast cancer at an as early stage as possible in order to reduce mortality.

Clinical examinations of the breasts and self-examination as a screening procedure have been poorly evaluated. There is only limited and indirect evidence that these methods could help in decreasing mortality due to breast cancer[2]. As mentioned, small malignant lesions (<10 mm) will not be detected by palpation in the majority of cases. Kriege and co-workers showed a sensitivity of only 17.8% of clinical breast examination in a screening setting[6].

The most used imaging tool for screening at the moment is mammography. The sensitivity of mammography increases with the age of the woman. The younger the woman, the more glandular tissue there is, the denser the breasts are, and the lower the sensitivity of mammography. For women in the age group 40–50 sensitivity ranges from about 50% to 80%, while in the age group over 50 the sensitivity ranges from 70% to about 90%[33]. The sensitivity of mammography in the

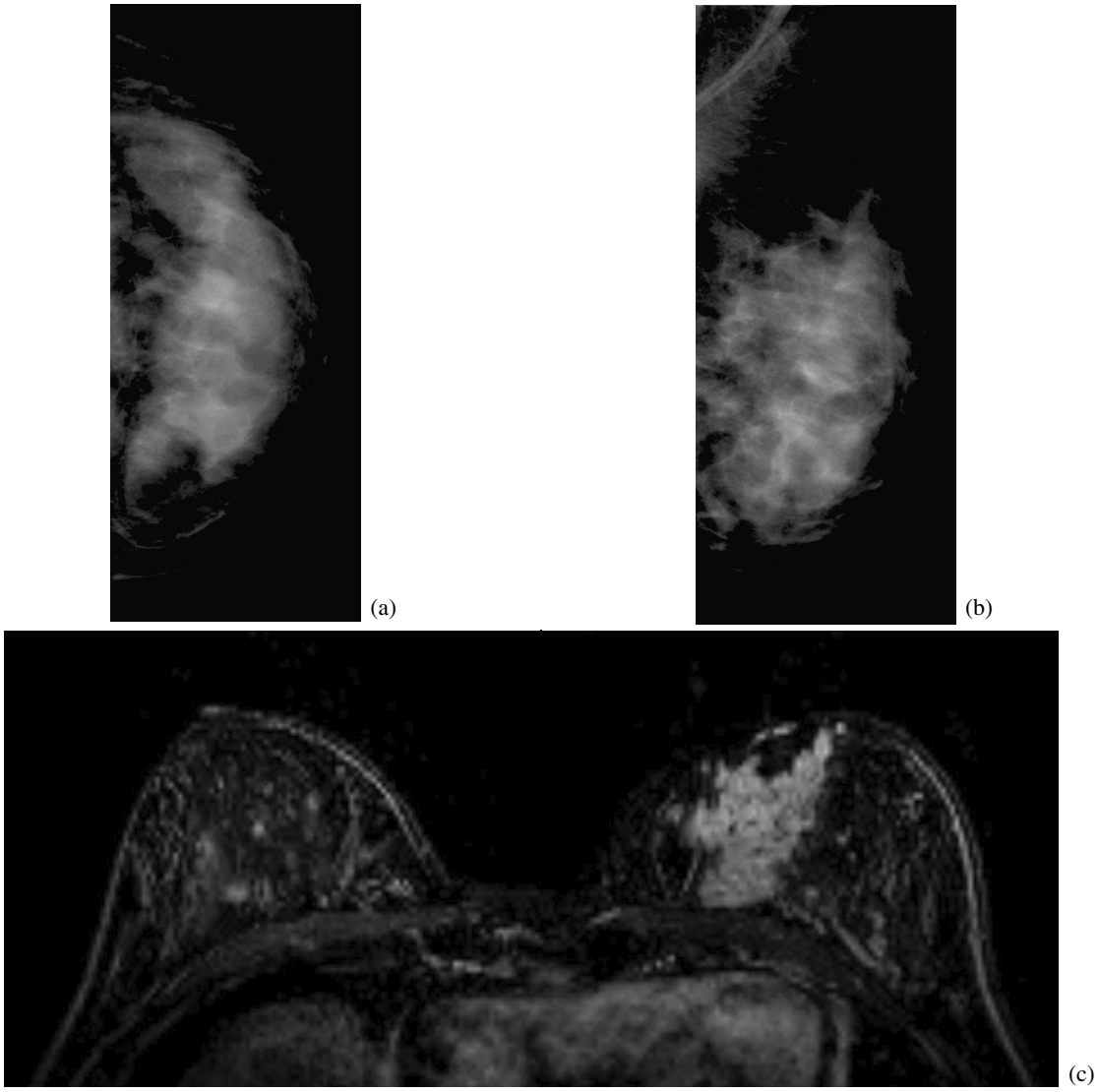

Figure 1 **(a), (b) The mammography of a 39-year-old woman obtained during annual screening because of a familial history of breast cancer. No abnormalities were seen. (c) The MRI examination obtained on the same day. Strong irregular enhancement in the medial part of the left breast was detected. Pathology revealed a DCIS grade 3.**

case of invasive lobular carcinoma (ILC) is lower than in women with invasive ductal carcinoma (IDC)[30].

In 1973, the breast cancer detection demonstration project (BCDDP) was started. In the subsequent 7 years more than 280 000 women were screened. The screening depicted about half of all breast cancers detected in the screened area. In addition, the distribution of stage was more favourable in the screened population than in a control group in that area, so overall long-term survival was also better[34]. In 1998 in the Netherlands a mortality reduction of 13% was reached in the age category 55–74 since the beginning of screening in 1990 with conventional mammography[35]. Other screening trials like the health insurance plan of New York (HIP-study) showed a mortality reduction of 30% in the screened group compared to the control group. Analysis of age specific mortality reduction indicates that screening for breast cancer has a special benefit in older women above the age of 50 and less in the younger age group. In addition, Tabar *et al.* showed that the likelihood of dedifferentiation of a tumour is much higher in women younger than 40 years[36]. Survival is also influenced by both tumour grade and the size of the tumour[36,37].

There is currently no evidence that ultrasound (US) has a role as a screening modality for breast cancer. The two most important roles of US are differentiation between cystic and solid lesions in the breast and US guided biopsy of solid breast lesions.

MRI of the breast is nowadays mostly performed as a dynamic investigation. The most currently used investigation technique is the FLASH 3D technique which includes one series of images pre-contrast and

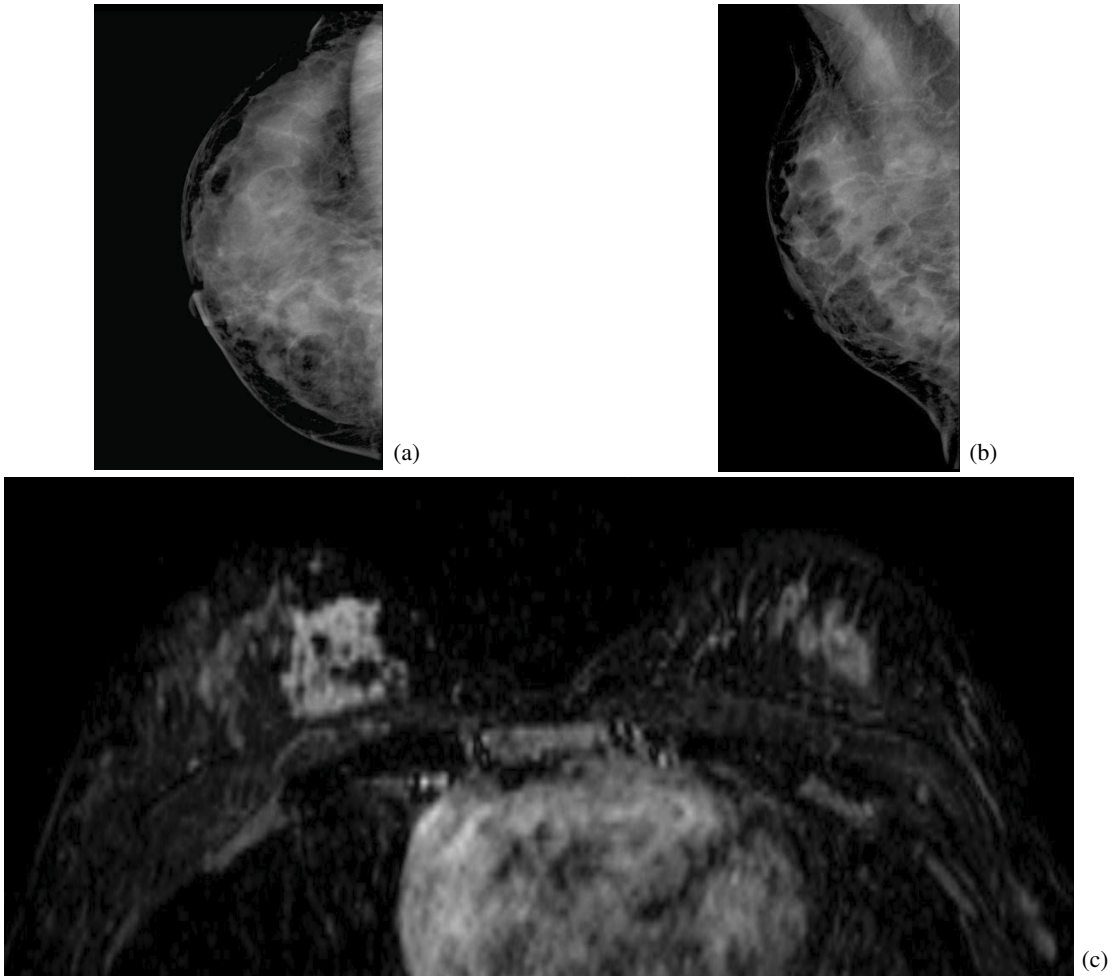

Figure 2 **(a), (b) The mammography of a 32-year-old woman obtained during annual screening because of a proven $BRCA_2$ gene carrier. Very dense glandular tissue was seen on mammography. (c) The MRI from the same day. In the medial part of the right breast an irregular strong enhancing area was seen. Pathology showed an invasive duct carcinoma.**

five series of images after intravenous administration of contrast medium containing gadolinium. MR images are evaluated according to morphology and kinetic behaviour of the lesions[38]. Smoothly outlined round or oval lesions tend more to be benign, while speculated lesions are more suspicious of a malignancy. If a lesion shows a wash out on kinetic behaviour, this is highly suspicious for a malignancy. If there is progress in signal intensity over time this is more characteristic for a benign lesion[38]. Although the sensitivity of MRI for detecting invasive breast cancer is more than 95%, the value in detecting DCIS, especially DCIS grade I, is lower[39]. DCIS grade 3 can usually be detected on MRI (Fig. 1). The sensitivity for DCIS is described by Orel *et al.*[40] to be in the range of 75%. Three grade I DCIS were missed. This is in comparison to the results of Boetes *et al.*[41], who also described a sensitivity of about 75% in this group. In a series of 17 patients, they missed four cases of DICS, 3 grade I and 1 grade III. The problem with screening with MRI is the relatively low specificity, which means a relatively high number of false-positive findings. Almost all women with a genetic predisposition for developing breast cancer are younger than the age of 50. So the value of screening with conventional mammography is doubtful in this group of women.

Especially in young women in a screening situation it is important to diagnose a malignancy as early as possible to increase survival.

Kuhl was the first to describe the results of MRI in a screening situation for women with an increased risk for developing breast cancer[7]. A group of 192 asymptomatic and six symptomatic women were evaluated. In the symptomatic group, MRI detected all malignancies. In the asymptomatic group of women, nine malignancies were found. MRI detected all nine, whereas mammography combined with US detected only four.

In the same year Tilanus-Linthorst described an asymptomatic group of 109 women with a 25% or more lifetime risk, in which 12 gene carriers also were included. In this group MRI detected three malignancies

occult on mammography[42]. A retrospective study in 2001 by Stoutjesdijk *et al.*, evaluated 75 women, of whom 20% were proven gene carriers. Thirteen malignancies in this group showed a cancer on MRI while mammography detected five[43].

In 2003, Morris and co-workers described a group of 367 women, retrospectively. MRI detected 14 more malignancies than mammography[44].

In 2004, the results of screening a group of 1909 women with both MRI and mammography were described by Kriege *et al.*[6]. In the LTR group of 15%–30%, the detection rate for cancer was 7.8 per 1000 women, in the LTR of 30%–50% the detection rate was 5.4 per 1000. However, in the group of carriers of $BRCA_{1/2}$ the incidence of malignancy was 26.5 per 1000 women. The overall sensitivity for the detection of breast cancer was 40% for mammography and 71.5% for MRI (Fig. 2). If only the invasive cancers were taken into account the sensitivity of mammography dropped to 33% and of MRI increased to 79%. In the MRISK study group 43% of all invasive malignancies were smaller that 10 mm, but in two selected control groups only, 14 and 12.5%, the tumour was smaller than 10 mm. The negative node status was also better in the MRISK group than in both control groups with 21.4% compared to 52.4 and 56.4%, respectively.

The results for the MRISK study group are confirmed by the MARIBS study[8]. They evaluated 649 women with a total of 1881 screens both with mammography and MRI. Sensitivity of mammography was 40% and for MRI this was 77%. The combination of both imaging techniques showed a sensitivity of 94%. The difference in sensitivity was especially seen in the gene carrier group. However, as stated by Liberman[45], any method of screening for breast cancer has the potential for both benefit and harm. Harm are the costs, anxiety, follow-up imaging and benign biopsies. The benefit of screening is especially the detection of a malignancy as early as possible. This may give a mortality reduction. Although prognosis of small breast cancers is better, the detection of a small cancer does not guarantee an improved survival rate. The real value of screening can only be proved by randomized controlled trials with death as an end point. However, this is no longer possible. The data published to date show that screening with MRI has benefit for the group of women at high risk for developing breast cancer. However, if a centre proceeds to screen with MRI it should follow technical and interpretative guidelines and there should be the possibility of performing MR guided biopsies[46,47].

Conclusion

In the screening of women with an increased risk for developing breast cancer detection needs to be done at a young age. Therefore mammography is of limited value. Because the sensitivity of MRI is high for detecting breast cancer and because this sensitivity is not influenced by the amount of glandular tissue present, as with mammography, MRI is the best modality available at this time for the screening of women with an increased risk for developing breast cancer.

References

[1] Visser O, Coebergh JWW, van Dijck JAAM *et al*., eds. Incidence of Cancer in the Netherlands 1998. Utrecht, the Netherlands: Netherlands Cancer Registry, 2002.

[2] Baines CJ, Miller AB, Bassett AA. Physical examination. Its role as a single screening modality in the Canadian National Breast Screening Study. Cancer 1989; 63: 1816–22.

[3] Chu KC, Tarone RE, Kessler LG *et al*. Recent trends in US breast cancer incidence, survival, and mortality rates. J Natl Cancer Inst 1996; 88: 1571–9.

[4] Nystrom L, Andersson I, Bjurstam N, Frisell J, Nordenskjold B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. Lancet 2002; 359: 909–19.

[5] Bedrosian I, Schlencker J, Spitz FR *et al*. Magnetic resonance imaging-guided biopsy of mammographically and clinically occult breast lesions. Ann Surg Oncol 2002; 9: 457–61.

[6] Kriege M, Brekelmans CT, Boetes C *et al*. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 2004; 351: 427–37.

[7] Kuhl CK, Schmutzler RK, Leutner CC *et al*. Breast MR imaging screening in 192 women proved or suspected to be carriers of a breast cancer susceptibility gene: preliminary results. Radiology 2000; 215: 267–79.

[8] Leach MO, Boggis CR, Dixon AK *et al*. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 2005; 365: 1769–78.

[9] Newman B, Mu H, Butler LM, Millikan RC, Moorman PG, King MC. Frequency of breast cancer attributable to BRCA1 in a population-based series of American women. JAMA 1998; 279: 915–21.

[10] Hall JM, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, King MC. Linkage of early-onset familial breast cancer to chromosome 17q21. Science 1990; 250: 1684–9.

[11] Narod SA, Feunteun J, Lynch HT *et al*. Familial breast-ovarian cancer locus on chromosome 17q12-q23. Lancet 1991; 338: 82–3.

[12] Struewing JP, Hartge P, Wacholder S *et al*. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 1997; 336: 1401–8.

[13] Whittemore AS, Gong G, Itnyre J. Prevalence and contribution of BRCA1 mutations in breast cancer and ovarian cancer: results from three US population-based case-control studies of ovarian cancer. Am J Hum Genet 1997; 60: 496–504.

[14] Szabo CI, King MC. Population genetics of BRCA1 and BRCA2. Am J Hum Genet 1997; 60: 1013–20.

[15] DeMichelle A, Weber BL. Inherited genetic factors. In: Diseases of the Breast. Harris JR, Lippman ME, Morrow M *et al*., eds. Philadelphia, PA: Lippincott Williams and Wilkins, 1999: 221–36.

[16] Easton DF, Bishop DT, Ford D, Crockford GP. Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. The Breast Cancer Linkage Consortium. Am J Hum Genet 1993; 52: 678–701.

[17] Wooster R, Neuhausen SL, Mangion J *et al*. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. Science 1994; 265: 2088–90.

[18] Ursin G, Henderson BE, Haile RW *et al*. Does oral contraceptive use increase the risk of breast cancer in women with BRCA1/BRCA2 mutations more than in other women? Cancer Res 1997; 57: 3678–81.

[19] Schubert EL, Lee MK, Mefford HC *et al*. BRCA2 in American families with four or more cases of breast or ovarian cancer: recurrent and novel mutations, variable expression, penetrance, and the possibility of families whose cancer is not attributable to BRCA1 or BRCA2. Am J Hum Genet 1997; 60: 1031–40.

[20] Teng DH, Bogden R, Mitchell J *et al*. Low incidence of BRCA2 mutations in breast carcinoma and other cancers. Nat Genet 1996; 13: 241–4.

[21] Wooster R, Bignell G, Lancaster J *et al*. Identification of the breast cancer susceptibility gene BRCA2. Nature 1995; 378: 789–92.

[22] Li FP, Fraumeni Jr JF, Mulvihill JJ *et al*. A cancer family syndrome in twenty-four kindreds. Cancer Res 1988; 48: 5358–62.

[23] Brownstein MH, Wolf M, Bikowski JB. Cowden's disease: a cutaneous marker of breast cancer. Cancer 1978; 41: 2393–8.

[24] Starink TM. Cowden's disease: analysis of fourteen new cases. J Am Acad Dermatol 1984; 11: 1127–41.

[25] Jeghers H, McKusick VA, Katz KH. Generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits; a syndrome of diagnostic significance. N Engl J Med 1949; 241: 993.

[26] Fisher B, Costantino JP, Wickerham DL *et al*. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998; 90: 1371–88.

[27] Page DL, Dupont WD, Rogers LW, Landenberger M. Intraductal carcinoma of the breast: follow-up after biopsy only. Cancer 1982; 49: 751–8.

[28] Page DL, Dupont WD, Rogers LW, Jensen RA, Schuyler PA. Continued local recurrence of carcinoma 15–25 years after a diagnosis of low grade ductal carcinoma in situ of the breast treated only by biopsy. Cancer 1995; 76: 1197–200.

[29] Contesso G, Mouriesse H, Friedman S, Genin J, Sarrazin D, Rouesse J. The importance of histologic grade in long-term prognosis of breast cancer: a study of 1010 patients, uniformly treated at the Institut Gustave-Roussy. J Clin Oncol 1987; 5: 1378–86.

[30] Boetes C, Veltman J, van DL, Bult P, Wobbes T, Barentsz JO. The role of MRI in invasive lobular carcinoma. Breast Cancer Res Treat 2004; 86: 31–7.

[31] Colditz GA, Hankinson SE, Hunter DJ *et al*. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med 1995; 332: 1589–93.

[32] Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. J Natl Cancer Inst 1993; 85: 25–31.

[33] Fletcher SW, Black W, Harris R, Rimer BK, Shapiro S. Report of the International Workshop on Screening for Breast Cancer. J Natl Cancer Inst 1993; 85: 1644–56.

[34] Bassett LW, Liu TH, Giuliano AE, Gold RH. The prevalence of carcinoma in palpable vs. impalpable, mammographically detected lesions. AJR Am J Roentgenol 1991; 157: 21–4.

[35] National Evaluation Team for Breast Cancer Screening. Nationwide breast cancer screening fully accomplished; results from the implementation phase 1990–1997. Ned Tijdschr Geneeskd 2000; 144: 1124–9.

[36] Tabar L, Duffy SW, Burhenne LW. New Swedish breast cancer detection results for women aged 40–49. Cancer 1993; 72(Suppl 4): 1437–48.

[37] Tabar L, Fagerberg G, Duffy SW, Day NE, Gad A, Grontoft O. Update of the Swedish two-county program of mammographic screening for breast cancer. Radiol Clin North Am 1992; 30: 187–210.

[38] Kuhl CK. MRI of breast tumors. Eur Radiol 2000; 10: 46–58.

[39] Boetes C, Mus RD, Holland R *et al*. Breast tumors: comparative accuracy of MR imaging relative to mammography and US for demonstrating extent. Radiology 1995; 197: 743–7.

[40] Orel SG, Mendonca MH, Reynolds C, Schnall MD, Solin LJ, Sullivan DC. MR imaging of ductal carcinoma in situ. Radiology 1997; 202: 413–20.

[41] Boetes C, Strijk SP, Holland R, Barentsz JO, Van Der Sluis RF, Ruijs JH. False-negative MR imaging of malignant breast tumors. Eur Radiol 1997; 7: 1231–4.

[42] Tilanus-Linthorst MM, Obdeijn IM, Bartels KC, de Koning HJ, Oudkerk M. First experiences in screening women at high risk for breast cancer with MR imaging. Breast Cancer Res Treat 2000; 63: 53–60.

[43] Stoutjesdijk MJ, Boetes C, Jager GJ *et al*. Magnetic resonance imaging and mammography in women with a hereditary risk of breast cancer. J Natl Cancer Inst 2001; 93: 1095–102.

[44] Morris EA, Liberman L, Ballon DJ *et al*. MRI of occult breast carcinoma in a high-risk population. AJR Am J Roentgenol 2003; 181: 619–26.

[45] Liberman L. Breast cancer screening with MRI—what are the data for patients at high risk? N Engl J Med 2004; 351: 497–500.

[46] Veltman J, Boetes C, Wobbes T, Blickman JG, Barentsz JO. Magnetic resonance-guided biopsies and localizations of the breast: initial experiences using an open breast coil and compatible intervention device. Invest Radiol 2005; 40: 379–84.

[47] Viehweg P, Heinig A, Amaya B, Alberich T, Laniado M, Heywang-Kobrunner SH. MR-guided interventional breast procedures considering vacuum biopsy in particular. Eur J Radiol 2002; 42: 32–9.